REMARKS

Claims 88-142, as amended, appear in this application for the Examiner's review and consideration. Claims 91, 114 and 137 were amended to recite a preferred electric field strength, while claims 95, 97 and 120 were amended to recite a preferred material for the substrate upon which the at least one biomolecule species is immobilized. For the reasons that follow, no new matter has been introduced and these amendments should be entered at this time.

The Office Action dated November 15, 2002 has been received and its contents carefully noted. The allowance of claims 108-121 and indication of allowable subject matter in claims 124 and 125 are acknowledged with appreciation. For the reasons that follow, it is believed that all claims are now in condition for allowance.

The rejection of claims 88-94, 98-100, 107, 122-123 and 126 under 35 USC §103(a) as being unpatentable over US patent 5,525,198 to Craig et al. (Craig) is respectfully traversed.

The Office action suggests that Craig teaches crystallization of biomolecules using electricity in a reactor containing a buffer solution with a pH (page 2 of the Office Action). Actually, Craig teaches the use of electrorheology for obtaining masses of biomolecules (col. 2, lines 26-28). Craig discloses that electrorheology requires inducing a dipole moment by subjecting the molecules to a strong electric field in the order of 1-10 kV/mm (col. 6, lines 12-15). The dipole moment is obtained as the protons inside the molecules are attracted to the negative pole of the electrical field and the electrons are attracted to the positive pole of the field (col. 2, lines 34-46). The polarized molecules then align relative to the electric field, positive dipole end to negative dipole end, to form a solid mass (e.g., col. 2, lines 47-57 and col. 4, lines 34-51).

In comparison to the present claims, Craig fails to teach or suggest rapid crystallization of biomolecules by generating a concentrated solution of the biomolecules in an isoelectric focusing buffer encompassing the pI of the biomolecules. This feature is expressly recited in current claims 88-94, 98-100 and 107. Furthermore, Craig certainly does not teach or even suggest use of an apparatus comprising a buffer chamber; at least one crystallization reactor comprising isoelectric focusing buffer and a device for generating an electrical field, as recited in claims 122-123 and 126.

Applicant traverses the Examiner's assertion that it would have been obvious to one of ordinary skill in the art to determine through routine experimentation the optimum, operable pI to the pH in Craig in order to allow for proper crystallization due to the electrical current (page 2 of the Office Action). Applicant points out that merely combining a determination of pI, as known in the art, with Craig would not result in rapid crystallization as taught by the present claims since Craig and the present invention work in a substantially different manner. Craig is based on electrorheology the principles of which are significantly different from isoelectric focusing, the latter being an important feature of the present claims. As detailed above, according to Craig, creating masses of biomolecules by electrorheology requires induction of dipole moments in a strong electrical field of 1-10 kV/mm to cause aggregation of the proteins. In contrast, the present invention as described by claims 88-94, 98-100, 107, 122-123 and 126 is based on performing isoelectric focusing on a solution of biomolecules within a crystallization reactor encompassing the pI of the biomolecule. Each biomolecule when driven into the volume of the reactor loses its charge and ceases moving in the electric field (e.g. paragraph [0100]). Accordingly, a concentrated solution or band (aggregate) of uncharged proteins is formed in the crystallization reactor. In this process of electrophoretical accumulation, which is very fast (typically occurring on the order of minutes), the accumulating biomolecules spread out within the crystallization reactor by diffusion resulting in rapid crystal nucleation and growth therein. This process does not require high voltage, in fact, it may be carried out efficiently in an electric field within the range of 50 - 2,000 V/cm (paragraph [0052] in the specification), a value that is up to 4 orders of magnitude lower than the electric field required for electrorheology according to Craig. Thus, the invention of Craig is incapable of forming a concentrated solution of uncharged biomolecules which forms crystals as it diffuses in the reactor. Stated otherwise, Craig teaches away from the present invention.

Moreover, although isoelectric focusing was widely used for protein separation and purification on the basis of their characteristic net electrical charge that varies with pH (e.g. paragraphs [005] and [102]), it is Applicant who has discovered that concentrating biomolecules in a solution, including a dilute solution, within a crystallization reactor by utilizing isoelectric focusing leads to rapid crystallization of the

biomolecules within the solution. In view of the above, independent claims 88 and 122 and dependent claims 89-94, 98-100, 107, 123 and 126 are patentable over Craig.

The rejection of dependent claims 95, 97, 127 and 129 under 35 USC §103(a) as being unpatentable over Craig et al. (US 5,525,198) in view of Sanjoh (US 6,174,365) is also respectfully traversed.

Claims 95 and 97 and claims 127 and 129 depend from independent claims 88 and 122, respectively. Thus, all of the elements of claims 88 and 122 are integral components of claims 95 and 97 and claims 127 and 129, respectively. As detailed above, Craig does not teach or suggest use of isoelectric focusing in a reactor for generating a concentrated uncharged solution of biomolecules that rapidly crystallizes or an apparatus for rapid formation of biomolecule crystals adapted for applying isoelectric focusing. In addition, Sanjoh fails to rectify the deficiencies of Craig. Sanjoh is directed to crystallizing macromolecules on a semiconductor substrate and does not teach or even suggest use of isoelectric focusing in a reactor for generating a concentrated uncharged solution of biomolecules that rapidly crystallizes. Thus, claims 95 and 97 and claims 127 and 129 are believed to be patentable over the combination of Craig and Sanjoh for the same reasons set forth above for independent claims 88 and 122.

Moreover, the substrate disclosed by Sanjoh is in fact a semiconductor substrate whose valence electrons are controlled, wherein the substrate has a plurality sites for holding a solution containing macromolecules (col. 4, lines 1-15). According to the teaching of Sanjoh, the macromolecules are not immobilized onto the substrate. In contrast, the one and only function of the substrate according to claim 95 is to maintain the biomolecules immobilized thereon.

Furthermore, the substrate in claims 97, 127 and 129 is not a complicated semiconductor substrate whose valence electrons are controlled. Conveniently, this substrate is simply intended for supporting the crystallization reactors according to claims 97, 127 and 129, and it may be a porous carrier substrate such as filter-paper, cotton or linen cloth, polymer or other suitable web materials to provide adequate strength (paragraph [0152] of the present application), and no complicated semiconductor substrates are required.

Applicants submit that one of ordinary skill in the art would not be motivated to combine the teachings of Sanjoh with that of Craig to arrive at the invention of claims 95, 97, 127 and 129. This is because the invention of Sanjoh is intended for crystallizing macromolecules on a semiconductor substrate, whereas that of Craig is specifically intended for crystallizing macromolecules by electrorheology. In contrast, the present invention relates to a different technique, namely, crystallizing biomolecules by performing isoelectric focusing in a crystallization reactor. Thus, Applicant submits that there would be no motivation for combining Sanjoh with Craig to arrive at the present invention, since the two references relate to substantially different techniques which in turn are substantially different from the invention of claims 95, 97, 127 and 129. Instead, these references teach away from each other as well as from the present invention. Accordingly, claims 95, 97, 127 and 129 are patentable over the combination of Craig and Sanjoh.

The rejection of dependent claims 96, 106, 128 and 130 under 35 USC §103(a) as being unpatentable over Craig (US 5,525,198) in view of Sanjoh (US 6,174,365) is also respectfully traversed. Claims 96 and 106 and claims 128 and 130 depend from independent claims 88 and 122, respectively. Thus, all of the elements of claims 88 and 122 are integral components of claims 96 and 106 and claims 128 and 130, respectively. As detailed above, neither Craig nor Sanjoh describe or suggest use of isoelectric focusing in a reactor for generating a concentrated uncharged solution of biomolecules that rapidly crystallize or an apparatus for rapid formation of biomolecule crystals adapted for applying isoelectric focusing. Moreover, as explained herein, claims 88 and 122 are non-obvious over Craig in view of Sanjoh. Accordingly, claims 96, 106, 128 and 130 are patentable over Craig in view of Sanjoh for the same reasons as set forth above for independent claims 88 and 122.

Furthermore, as noted above, the substrate in claims 96, 106, 128 and 130 is not a semiconductor substrate whose valence electrons are controlled as taught by Sanjoh. Rather it is a capillary (claims 96 and 106) or it is selected from the group of pH immobilized gradient strips, pH membranes and pre-cast gels (claims 106 and 128). Neither Craig nor Sanjoh describe or suggest a substrate which is a capillary, pH immobilized gradient strip, pH membrane or a pre-cast gel. Applicant respectfully

reiterates that one of ordinary skill in the art would not be motivated to combine the teachings of Sanjoh with that of Craig to arrive at the invention of claims 96, 106, 128 and 130 because the two references relate to substantially different techniques which in turn are substantially different from rapid crystallization in a crystallization reactor based on isoelectric focusing, a crucial feature of the present claims. Hence, claims 96, 106, 128 and 130 are patentable over Craig in view of Sanjoh.

The rejection of dependent claims 101-105 under 35 USC §103(a) as being unpatentable over Craig et al. (US 5,525,198) in view of Sanjoh (US 6,174,365) and Arnowitz et al (US 2004/0033166) also is respectfully traversed. Claims 101-105 depend from independent claim 88. Thus, all of the elements of claim 88 are integral components of claims 101-105. Claims 101-105 add the feature that rapid crystallization according to claim 88 occurs in a plurality of crystallization reactors comprising different or similar protein species, different or similar isoelectric focusing buffers wherein the plurality of crystallization reactors may be isolated from one another or joined. As detailed above, neither Craig nor Sanjoh teaches or suggests use of isoelectric focusing in a reactor for generating a concentrated uncharged solution of biomolecules that rapidly crystallize. Arnowitz is directed to robotic dialysis devices adapted for crystal growth of, *inter alia*, biomolecules and automated methods for using same to monitor crystal growth in large scales. The device comprises a plurality of dynamic dialysis units and a reagent reservoir wherein each dialysis unit comprising: a sample chamber; at least one sensor sensing physical or chemical attributes of a sample in the sample chamber of each unit and producing a corresponding output signal; a control system receiving the output signal; and an analysis system that analyzes the output signals. It is difficult to understand how the teaching of Arnowitz can be combined with that of Craig or Sanjoh for establishing obviousness of claims 101-105. Stated otherwise, there is nothing in the disclosure of Arnowitz that rectifies the deficiencies of Craig, Sanjoh or their combination.

Furthermore, the method disclosed in claims 101-105 does not include use of dynamic dialysis units for monitoring the generation of crystal formation in a plurality of crystallization reactors. Rather, as detailed above, the method of claims 101-105 applies isoelectric focusing in a plurality of crystallization reactors thereby enabling large

scale rapid crystallization of a plurality of different or similar protein species. Applicant respectfully submits that one of ordinary skill in the art would not be motivated to combine the teachings of Sanjoh with that of Craig and Arnowitz to arrive at the invention of claims 101-105 because the three references relate to substantially different techniques which in turn are substantially different from rapid crystallization in a crystallization reactor based on isoelectric focusing, a crucial feature of the present claims. Instead, these documents teach away from each other and could only be combined using Applicant's specification as a guide, a procedure that is improper in view of numerous Federal Circuit decisions. Even if combined as suggested, one would not arrive at the invention defined by claims 101-105. Accordingly, claims 101-105 are patentable over the combination of Craig, Sanjoh and Arnowitz.

The rejection of dependent claims 131-142 under 35 USC §103(a) as being unpatentable over Craig et al. (US 5,525,198) in view of Sanjoh (US 6,174,365) and Arnowitz et al (US 2004/0033166) is likewise respectfully traversed. Claims 131-142 depend from independent claim 122. Thus, all of the elements of claim 122 are integral components of claims 131-142. As explained herein, base claim 122 is non-obvious over the cited prior art. Since the base claim is non-obvious, claims 131-142 are non-obvious. Specifically, claims 131-142 specify types of materials that may be used for forming the various components of the apparatus of claim 122. Applicant respectfully reiterates that neither Craig nor Sanjoh or Arnowitz teaches or suggests an apparatus adapted for applying isoelectric focusing and for rapid formation of biomolecule crystals. Applicant respectfully submits that it is the various components of the apparatus described in independent claim 122 which make the apparatus proper for rapid crystallization of biomolecules within a solution by isoelectric focusing. Accordingly, claims 131-142 are patentable over Craig in view of Sanjoh and Arnowitz.

Finally, a Supplemental Information Disclosure Statement is enclosed. It is respectfully submitted that the references cited on this Statement are not material to the patentability of the present claims and the Examiner's acknowledgement of the same would be appreciated by signing and retuning a copy of the enclosed Form PTO 1449.

In view of the above, it is respectfully submitted that all current rejections have been overcome and should be withdrawn. Accordingly, the entire application is

believed to be in condition for allowance, early notice of which would be appreciated. Should the Examiner not agree, then a personal or telephonic interview is respectfully requested to discuss any remaining issues and expedite the eventual allowance of this application.

Respectfully submitted,

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